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Chapter 6 - Hypothalamic-Pituitary-Adrenal (HPA) axis  
to Depression and Type 2 Diabetes- Oxford University Press

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## **ABSTRACT**

Increased adrenocortical secretion of hormones, primarily cortisol in depression, is one of the most consistent findings in neuropsychiatry. The maintenance of the internal homeostatic state of an individual is facilitated by the ability to circulate glucocorticoids to exert negative feedback on the secretion of hypothalamic-pituitary-adrenal (HPA) hormones through binding to mineralocorticoid (MR) and glucocorticoid (GR) receptors, thus limiting the vulnerability to diseases related to psychological stress in genetically predisposed individuals. The HPA axis response to stress can be thought of as a crucial part of the organism's response to stress: acute responses are generally adaptive, but excessive or prolonged responses can lead to deleterious effects. A spectrum of conditions may be associated with increased and prolonged activation of the HPA axis, including depression, poorly controlled diabetes mellitus, and metabolic syndrome. HPA axis dysregulation and hypercortisolemia may further contribute to a hyperglycaemic or poorly controlled diabetic state.

**Keywords:** hypothalamic–pituitary–adrenal (HPA) axis, cortisol, mineralocorticoid (MR) receptors, glucocorticoid (GR) receptors, depression, diabetes

## **A. INTRODUCTION**

The relationship between stress and affective(mood) disorders is a strong example of a field of study that can be best understood from an integrative perspective. During acute stress, adaptive physiological responses occur, including increased adrenocortical hormone secretion, primarily cortisol. Whenever an acute interruption of this balance occurs, illness may result. Particularly interesting are psychological stress (i.e., stress in the mind) interactions with the nervous, endocrine, and immune systems. It is now broadly accepted that psychological stress may change the internal homeostatic state of

an individual [1].

During acute stress, adaptive physiological responses occur, which include hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis. Whenever there is an acute interruption of this balance, illness may result. The social and physical environments have an enormous impact on our physiology and behaviour, and they influence the process of adaptation or ‘allostasis’. It is correct to state that at the same time that our experiences change our brain and thoughts, namely, changing our mind, they are also changing our neurobiology [2].

## **B. PHYSIOLOGY OF THE HPA AXIS**

The HPA axis constitutes one of the major endocrine systems that maintains homeostasis when the organism is challenged or stressed. Activation of the HPA axis is perhaps the most important endocrine component of the stress response [3]. Abnormal activation of the HPA axis, as well as increased circulating levels of cortisol, is one potential explanation for many of the features of depression, and many previous studies have described an impaired HPA negative feedback, leading to hypercortisolemia, in the most severe forms of depression [4].

Cortisol mediates its action, including feedback regulation of the HPA axis, through two distinct intracellular corticosteroid receptor subtypes in the brain: the type-I, high affinity, mineralocorticoid receptor (MR) and type-2, glucocorticoid receptor (GR) [5]. The type-I receptor (MR) has a limited distribution, and it is found in relatively high density in the hippocampus and sensory and motor sites outside the hypothalamus. The expression of type-II receptors (GR) is more widespread, and they are found in the hippocampus, the amygdala, the hypothalamus, and the catecholaminergic cell bodies of the brain stem [6]. There is a theory that suggests that a GR defect may mediate the impaired negative feedback thought to cause hypercortisolemia in depression [7].

Under basal levels of cortisol, negative feedback is mediated mainly through the MR in the hippocampus, whereas under stress and high cortisol concentrations, feedback is mediated by the less sensitive GR in the hippocampus, hypothalamus, and pituitary gland. The balance in these MR- and GR-mediated effects on the stress system is of crucial importance to the set point of the HPA axis activity [5].

It is proposed that the maintenance of corticosteroid homeostasis and the balance in MR-/GR-mediated effects limit vulnerability to stress-related diseases

in genetically predisposed individuals. Stress-induced activation of the HPA axis generally involves stimulated release of corticotropin-releasing factor (CRF) from the paraventricular nucleus (PVN) of the hypothalamus into the portal venous circulation, where CRF stimulates the synthesis of proopiomelanocortin, the precursor of adrenocorticotrophic hormone (ACTH) from anterior pituitary cells. Arginine-vasopressin (AVP) is a potent synergistic factor with CRF in stimulating ACTH secretion [8].

In the hypothalamus, the PVN receives fibers from a number of brain areas, notably the brain stem and limbic system (e.g., amygdala and the septal areas). It is thought that these afferents may be important in HPA responses to behavioural and emotional stimuli and may play a role in corticosteroid feedback. Several peptides are released alongside and interact with CRF at the level of the anterior pituitary and alter the stimulatory action of ACTH secretion [9] Increases in circulating ACTH stimulate glucocorticoid release from the adrenal cortex (see Fig. 1).

INSERT FIGURE 1
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The division of the adrenal cortex into separate layers is important since zones produce different steroids [10]. Table 1 summarises the adrenal steroids. Cortisol is produced by the zona fasciculata at the rate of 12–15 mg/m<sup>2</sup> of body surface area per day. However, more than 90% of the circulating cortisol is bound to corticosteroid-binding globulin

(CBG) in humans and rodents. Also, it has been observed that both exogenous glucocorticoid administration and endogenous increases in plasma cortisol (for example, Cushing's syndrome) result in a 30–40% decrease in the plasma CBG concentration. Thus, CBG levels fluctuate according to glucocorticoid concentration [11-12].

INSERT TABLE 1
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Adrenocorticotrophic hormone is secreted in irregular bursts throughout the day, and plasma cortisol tends to rise and fall in response to this pulsatile secretion. In humans, the bursts are most frequent in the early morning and least frequent in the evening. The biological clock responsible for the diurnal ACTH rhythm is thought to be located in the suprachiasmatic nuclei of the hypothalamus. Changes in the activity of these neurones increase the release of CRF and AVP by the PVN during usual times of peak activity. Consequently, it is thought that the secretion of CRF and AVP also follows a pulsatile pattern. However, CRF levels in human peripheral plasma are very low and do not exhibit circadian variation, and therefore, these levels cannot be used reliably to assess hypothalamic CRF release relevant to the HPA axis. An important feature is the intrinsic rhythmicity of the HPA axis with regard not only to the diurnal variation but also to the pulsatility, which is comparable to the rhythm found within the reproductive and growth hormone axes [10]. A wide variation in cortisol levels is observed among individuals in response to a stressor. This variability is so marked that in any one individual, it is not always possible to distinguish a stress response from a spontaneously occurring pulse. Young and Altemus [13] put forward a totally different hypothesis that acute stressors simply “advance” a spontaneous cortisol pulse rather than activate cortisol release as an independent variable, thereby acting as a synchronizer or “zeitgeber” for the ultradian cortisol rhythm, whose effectiveness will depend on a number of variables that control the individual's

endogenous rhythm. Finally, pulsatility analysis enables us to examine multiple aspects of the control of the HPA axis, extending our understanding well beyond mean cortisol levels [13].

Glucocorticoids control their own synthesis and release by completing a negative feedback loop at the level of the anterior pituitary, hypothalamus, and other higher centres, including the mesencephalic reticular formation. The circulating concentration of cortisol is a major influence at both the hypothalamic and pituitary levels (see Table 2). The negative feedback mechanisms constitute a rate-sensitive fast feedback system and a delayed feedback system. Fast feedback is proportional to the rate of rising of steroid concentrations and perhaps serves to limit the amplitude of the response. In contrast, delayed feedback is related to the ambient concentration of corticosteroid and is frequently the consequence of repeated or continuous administration of high doses of glucocorticoids. Delayed feedback may persist for days or weeks after the steroid treatment is withdrawn [9-11].

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**B.1. THE GLUCOCORTICOID RECEPTORS**

Steroid hormones are small, lipid-soluble ligands that diffuse across cell membranes. Unlike the receptors for peptide hormones, which are located in the cell membrane, the receptors for these ligands are localised in the cytoplasm. In response to ligand binding, steroid hormone receptors translocate to the nucleus, where they regulate the expression of certain genes by binding to specific hormone response elements (HREs) in their regulatory regions. Type-I receptors are thought to be involved in controlling the basal expression of CRF and AVP at the nadir of diurnal ACTH secretion and in controlling peak ACTH secretion [14-15]. Type-II receptors are considered to be involved in control

of stress-induced ACTH secretion. According to the "nucleocytoplasmic traffic" model of GR action, the GR in its "unactivated" form resides primarily in the cytoplasm in association with a multimeric complex of chaperone proteins including several heat shock proteins (HSPs). After being bound by steroid, the GR undergoes a conformational change, dissociates from the chaperone protein complex, and translocates from the cytoplasm to the nucleus, where it either binds to glucocorticoid response elements (GREs) on DNA or interacts with other transcription factors. Glucocorticoid response elements can confer either positive or negative regulation of the genes to which they are linked. Glucocorticoid receptors have a low affinity but high capacity for cortisol and are very responsive to changes in cortisol concentrations [14-15].

Studies on the subcellular localisation of the MR have been controversial. In the lack of corticosteroid hormone, MR is present both in the cytoplasm and in the nucleus. However, the presence of corticosteroid hormone induced a rapid nuclear accumulation of the MR. The MR has a high affinity for endogenous glucocorticoids: the in vitro dissociation constant/ionisation constant ( $K_d/K_i$ ) is 0.13 nM for cortisol binding to human MR and 0.5 nM for corticosterone binding to mouse MR. In contrast, the GR has a low affinity for endogenous glucocorticoids: the in vitro  $K_d/K_i$  is 15 nM for cortisol binding to human GR and 5 nM for corticosterone binding to mouse GR. Under basal levels of cortisol, negative feedback is mediated mainly through the MR in the hippocampus, whereas under stress and high cortisol concentrations, the less sensitive GR in the hippocampus, hypothalamus, and pituitary gland come into play. The balance in these MR- and GR-mediated effects on the stress system is of crucial importance to the set point of the HPA axis activity [16]. Spencer et al. [14] and de Kloet et al. [5] have clarified that GR activation is necessary for the HPA feedback regulation when levels of glucocorticoids are high (response to stress, circadian peak) but that MR also plays an important role by



modulating GR-dependent regulation.

## **B.2. BRAIN CORTICOSTEROID BALANCE IN HEALTH AND DISEASE**

Data on corticosteroid receptor diversity led de Kloet et al. [5] to a working hypothesis that in rodents, “tonic influences of corticosterone are exerted via hippocampal MRs, while the additional occupancy of GRs with higher levels of corticosterone mediates feedback actions aimed to restore disturbances in homeostasis”. This proposal provides a receptor-based version of Selye's classical “pendulum hypothesis” on opposing effects of mineralocorticoids and glucocorticoids in host defense. In humans, while MRs are thought to be involved in the tonic inhibitory activity within the HPA axis, GRs appear to “switch off” cortisol production at times of stress [17]. According to Pace and Spencer [18], MRs may be necessary for glucocorticoid regulation of HPA axis activity during mild stressors but not during stressors that result in a stronger corticosterone response. It is proposed that the maintenance of corticosteroid homeostasis and the balance in MR/GR-mediated effects limit vulnerability to stress-related diseases in genetically predisposed individuals [5].

## **B.3. STATES ASSOCIATED WITH HYPERACTIVATION**

Hyperactivity of the HPA axis in depression is one of the most consistent findings in psychiatry. A significant percentage of patients with major depression have been shown to exhibit increased concentrations of cortisol in plasma, urine, and cerebrospinal fluid

(CSF); an exaggerated cortisol response to adrenocorticotrophic hormone (ACTH); and an enlargement of both the pituitary and adrenal glands [4]. Adrenal hypertrophy in patients with depression has been demonstrated, and this finding likely explains why the cortisol response to CRF is similar in subjects with depression and control subjects because the enlarged adrenal gland is capable of compensating for the blunted ACTH response to CRF commonly observed in patients with depression [16]. Increased pituitary volume in these patients has also been described, and it has also been considered a marker of HPA axis activation. The first episode of a psychosis has also been found to be associated with a larger pituitary volume, and it has been suggested that this is due to activation of the HPA axis; the smaller pituitary volume in subjects with established psychosis could also be the consequence of repeated episodes of HPA axis hyperactivity. In general, HPA axis changes appear to be state-dependent, tending to improve upon resolution of the depressive syndrome. In fact, previous studies have described an impaired HPA negative feedback, leading to hypercortisolemia [16-19].

A spectrum of other conditions may be associated with increased and prolonged activation of the HPA axis, including anorexia nervosa with or without malnutrition, obsessive-compulsive disorder, panic anxiety, chronic active alcoholism, alcohol and narcotic withdrawal, poorly controlled diabetes mellitus, and hyperthyroidism [20]. Another group of states is characterised by hypoactivation of the stress system, rather than sustained activation, in which chronically reduced secretion of CRF may result in pathological hypoarousal and an enhanced HPA negative feedback. Patients with posttraumatic stress disorder, atypical depression, seasonal depression, and chronic fatigue syndrome fall into this category [21], see figure 2.

INSERT FIGURE 2
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The dysregulations situate themselves at different levels of the HPA axis, and the

experimental findings can be classified under basal hormonal changes, postmortem findings, and results from imaging studies and functional tests. Theories as to the causes of abnormal HPA axis function in depression are that it is related to either (a) increased central drive at the hypothalamic level or (b) downregulation of GRs. Taking the first theory, it has been suggested that hypercortisolism represents a defect at or above the level of the hypothalamus, resulting in the hypersecretion of CRF and AVP [4]. Corticotropin-releasing factor itself has behavioural effects in animals that are similar to those seen in patients with depression including alterations in activity, appetite, and sleep [21]. The second theory suggests that a defect of GRs may also explain the hypercortisolemia seen in depression, via impaired negative feedback control of the HPA axis by glucocorticoids. Various research groups have suggested that the overactivity of the HPA axis in depression may be due to an abnormality of the GR at the limbic–hippocampal level [7-10]. This abnormality then results in a defect in or resistance to glucocorticoid. In fact, several findings in depression are consistent with an abnormality of the GR. Most notably, patients with depression fail to show most of the physical symptoms of corticosteroid excess, despite the frequent presence of hypercortisolism, suggesting that peripheral GRs may be abnormal or insensitive in depression. Consistent with the fact that GR is more important in the regulation of the HPA axis when endogenous levels of glucocorticoids are high [5] and with the fact that patients with major depression exhibit impaired HPA negative feedback in the context of elevated circulating levels of cortisol [16], a number of studies have described reduced GR function in patients with depression (GR resistance) and have concluded that antidepressants act by reversing these putative GR changes [16,22-23].

Because a wide variety of stressors reliably activate the HPA axis and because glucocorticoids are the end-products of HPA axis activation, these hormones have been

most commonly seen as the agents provocateurs, or even in extreme cases as the physical embodiment, of stress-induced pathology [16,22-23]. Indeed, it has been suggested that prolonged overproduction of glucocorticoids, whether as a result of ongoing stress or a genetic predisposition to HPA axis hyperactivity, damages brain structures (especially the hippocampus) essential for HPA axis restraint. Such damage, in turn, has been hypothesised to lead to a feed-forward circuit in which ongoing stressors drive glucocorticoid overproduction indefinitely: the “glucocorticoid cascade hypothesis”. Because of the capacity of high concentrations of glucocorticoids to disrupt cellular functioning in ways that can lead to a host of ills, this glucocorticoid overproduction is believed to contribute directly to many of the adverse behavioural and physiological sequelae associated with chronic stress [24-25].

#### **B.4. ASSESSING THE IMPAIRED HPA NEGATIVE FEEDBACK**

Functioning of the HPA axis can be assessed under basal as well as under challenged conditions. Basal cortisol mainly reflects adrenal functioning, whereas several challenge paradigms target different levels of the HPA axis [6-11]. Cortisol is secreted with a pulsatory diurnal rhythm, with a peak (average increase of 50%) approximately 30min after awakening and a progressive decline during the day with lowest levels around midnight. Basal cortisol may be assessed in several bodily fluids such as saliva, urine, blood (serum or plasma), and cerebrospinal fluid. Whereas salivary free cortisol and urinary free cortisol consist almost entirely of the (free) biologically active fraction, in blood, less than 10% of the cortisol is free. The major part is bound to cortisol-binding globulin or other proteins and, therefore, biologically inactive. A distinction can be made between psychosocial stress challenges and pharmacological stress challenges. Examples of the

psychosocial stress challenges are cognitive stress challenges, challenges using trauma related acoustic stimuli, or trauma scripts. The most often used psychosocial stress challenge is the Trier Social Stress Test (TSST) that combines social-evaluative threat and uncontrollability [26].

The dexamethasone suppression test (DST) was the first and is, to date, the most studied biological marker in research on depressive disorders. In 1968, Bernard Carroll and colleagues showed that patients with depression fail to suppress plasma cortisol to the same extent as controls without depression. This impaired feedback inhibition by dexamethasone has been demonstrated in patients with depression by a variety of studies, many occurring in the 1970s and the 1980s. However, in the 1990s, several studies found that the sensitivity of the DST in the diagnosis of the DSM-III defined the melancholic subclass of major depression was only approximately 35–45%, although the specificity was higher at approximately 70–89% [27-28]. A meta-analysis to determine the significance of differences in rates of no suppression of cortisol indicated a high probability that a greater rate of cortisol no suppression occurs in psychotic depression (64% versus 41% in patients without psychosis). The DST/CRH combines the DST and the CRH stimulation test in the dexamethasone suppression/corticotropin-releasing hormone stimulation (DEX/CRH) test [27-28]. Watson et al. [29] compared the use of the DEX/CRH test and the DST in patients with mood disorders and controls, and suggested that the two tests measure common pathology but that the DEX/CRH test is more specific and hence has better diagnostic utility. Nevertheless, the DEX/CRH test remains limited by the pharmacokinetic profile of dexamethasone and the lack of MR activity.

Prednisolone is a synthetic glucocorticoid that, like dexamethasone, is widely used as an anti-inflammatory and immunosuppressive drug. Prednisolone mimics cortisol in many

ways. Like cortisol, it binds to CBG, and its half-life is similar to that of cortisol. However, the most important of these similarities is that prednisolone and cortisol are similar in their abilities to bind and activate the GR and the MR [17,30-32]

## **C- HPA AXIS IN DEPRESSION AND IMPLICATIONS FOR DIABETES**

Once cortisol is released from the adrenal cortex in response to ACTH stimulation, it functions to increase blood glucose levels through its action on glycogen, protein, and lipid metabolism. In the liver, cortisol stimulates gluconeogenesis and, in adipose tissue, activates lipolysis and free fatty acids (FFA) to be released into the circulation. Cortisol also has a permissive effect on glucagon and catecholamine action, thereby contributing to insulin resistance and increased blood glucose levels at the expense of glycogen, protein, and lipid storage [33-34]

There is growing evidence that depression may cause major life-threatening and disabling diseases, such as diabetes mellitus [33]. The metabolic syndrome is a clustering of risk factors associated with a particularly high risk of cardiovascular events and diabetes.

Dysregulation of the HPA-axis is typically associated with chronic stress, and some studies have described an association between depression and high cortisol levels and, in turn, elevated levels of cortisol have been related to metabolic syndrome components such as abdominal obesity and glucose intolerance [34]

There is now evidence that insulin exerts important functions in neural development and synaptic plasticity[35]. These findings have led to the hypothesis that insulin insufficiency may lead to the defects in neurocognition commonly observed in depression. Disrupted control of adrenocorticotrophic hormone (ACTH) release from pituitary corticotrophs and direct stimulation of corticotropin-releasing hormone of the adrenal gland with or without

the release of ACTH leads to hyperactivation of the HPA in patients with diabetes. Furthermore, the impairment of glucocorticoid negative feedback sensitivity in patients with diabetes also results in increased activity of the HPA axis: following glucocorticoid administration, these patients exhibit a greater incidence of no suppression of pituitary–adrenal activity compared with non-diabetic individuals[36]. Corticosteroids have been demonstrated to exert a tonic inhibitory control of hippocampal 5-HT1A receptors; this finding is of particular salience given the serotonin deficiency that occurs in depression. Once established, the HPA axis dysregulation and hypercortisolemia may further contribute to a hyperglycemic or poorly controlled diabetic state and has been associated with increased chronic complications of diabetes in adult studies [37]

There are two possible mechanisms underlying the association between Type 2 diabetes and the onset of depression. First, biochemical changes associated with diabetes could account for the increased risk of depression [38] For example, hyperglycemia and hyperinsulinemia increase the activity of the hypothalamic-pituitary-adrenal axis, inducing arousal of the nervous system, which in turn may promote depression [39]. Second, depression in patients with diabetes may be viewed as the result of the burden of the disease. This is supported by the finding that when the burden of diabetes increases, the probability of mood symptoms increases as well [40]

Patients with present diabetes alterations of the HPA axis negative feedback [41] suggestive of an impairment of corticosteroid receptor sensitivity. HPA axis disturbance seems to be particularly important for people with diabetes since the degree of cortisol secretion is related to the presence and number of diabetes complications[42]

At baseline, diabetes patients had increased glucocorticoid, but normal mineralocorticoid sensitivity in the presence of hypercortisolemia. The action of dexamethasone—which

exclusively binds to GR — and of prednisolone—which binds to both GR and MR — is respectively a proxy for glucocorticoid and mineralocorticoid sensitivity [17, 32] Such disturbance in the regulation of the HPA axis may contribute to deterioration in diabetes by enhancing the effect of cortisol and its anti-insulin actions, including the inhibition of glucose uptake in adipocytes and fibroblasts, increasing hepatic gluconeogenesis, sensitizing the liver to catecholamines and glucagon, and elevating blood glucose [43]. Our review suggests that in diabetes the ability to match the body's response to a stressor involves modulation of corticosteroid receptor sensitivity, an evidence of insufficient corticosteroid signalling. Moreover, insufficient corticosteroid signalling may also increase arousal and thus play a role in stress-related pathology.

#### **D- CONCLUSION**

Diabetes is associated with a lack of stress-induced modulation of glucocorticoid and mineralocorticoid sensitivity in the HPA axis. Emphasis on modulating glucocorticoids in stress-related pathology encourages the development of therapeutic strategies to modulate glucocorticoid-signalling pathways.

In conclusion, our review suggests a synergistic relationship between depression, cortisol, and diabetes. Persons with hypercortisolemic depression, in particular, may be at risk for having the metabolic syndrome, and therefore have an increased risk of developing diabetes.

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